PREPARING METHOD OF CHIRAL ESTER

BACKGROUND OF THE INVENTION

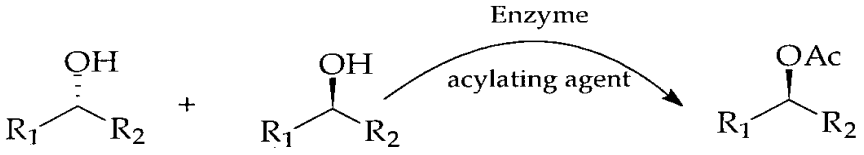
Field of the Invention

The present invention relates to a method for preparing a chiral ester and more particularly, the method for preparing an optically pure chiral ester from a racemic alcohol at a high yield.

Recently, studies for using a metal or an enzyme as a catalyst have been increased in asymmetric syntheses. It has been widely known to use an enzyme as a catalyst for kinetic resolution of a racemic mixture in organic syntheses. A variety of effective methods for hydrolysis of an ester and acylation of an alcohol in the presence of lipase as a catalyst has been reported.

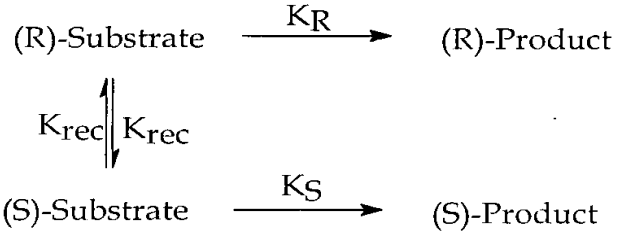
Kinetic resolution is the fact that the two enantiomers react at different rates with a chiral addend. An effective kinetic resolution is the enantioselective conversion from a racemic mixture to an optically pure product as shown in scheme 1, leaving the other enantiomer in a reaction medium.

Scheme 1

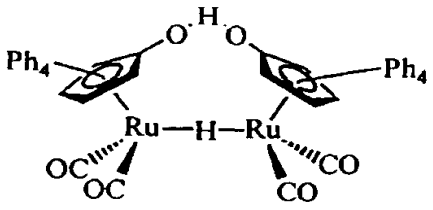


It is well known to prepare a chiral ester from a racemic alcohol by kinetic resolution using esterase. It is possible to obtain an optically pure ester but a maximum yield of this reaction is limited to 50% as shown in scheme 1. Therefore, dynamic kinetic resolution performing kinetic resolution and racemization of an alcohol simultaneously is introduced to resolve such problems (scheme 2).

Scheme 2



The well-known example of a dynamic kinetic resolution is the reaction by using ruthenium complex expressed in the following structure and lipase (Novozym 435) [B. A. Persson, A. L. E. Larsson, M. L. Ray, and J. E. Backvall, *J. Am. Chem. Soc.* 1999, **121**, 1645].



Because racemization of a starting material is performed simultaneously with kinetic resolution, the effectiveness of the starting material is very high and thus, yield of obtaining (R) or (S) enantiomer is theoretically 100%. However, even if the optical purity of a chiral ester obtained by dynamic kinetic resolution is 99 e. e.%, 12 to 40% of ketone as a by-product is produced.

SUMMARY OF THE INVENTION

Therefore, an object of the present invention is to provide a process for preparing an optically pure chiral ester from a racemic alcohol by dynamic kinetic resolution with minimum production of a ketone.

Detailed Description of the Invention

A process for preparing a chiral ester of the present invention is

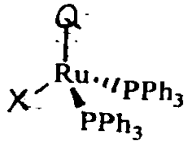
characterized by reacting:

a racemic alcohol;

a ruthenium complex selected from the group consisting of compounds 1, 2 and 3 expressed in formulas 1 to 3 to activate racemization of said racemic alcohol;

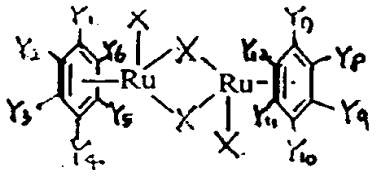
a lipase to acylate selectively one of enantiomers of said racemic alcohol; and

an acyl donor group to supply acyl group to said lipase,



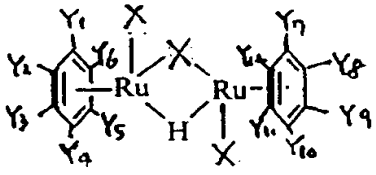
(1)

wherein Q is  or  ; and X is Br, Cl or I;



(2)

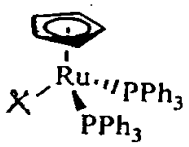
wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I;



(3)

wherein Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, Y_{11}, and Y_{12} are independently a hydrogen atom or C_1-C_5 alkyl group; and X is Br, Cl or I.

Said ruthenium complex is selected from the group consisting of the compounds 5 to 12 expressed in the following formulas 5 to 12,



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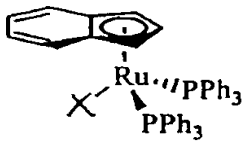

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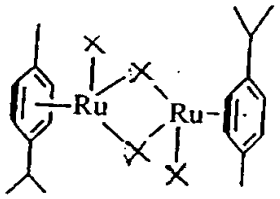

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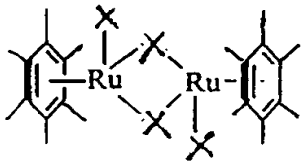

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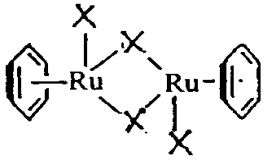

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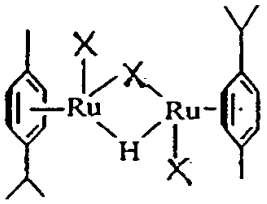

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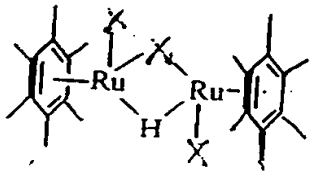

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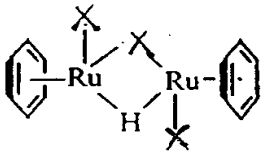


(12)

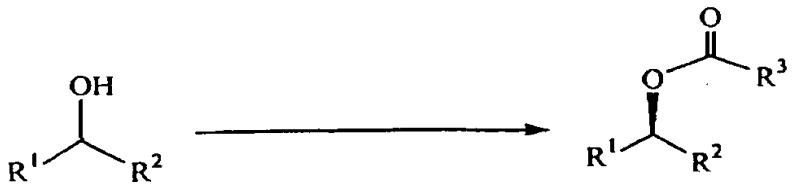
wherein X is Cl, Br or I, the most preferably Cl.

Preferred content of ruthenium complex is 0.1 to 5 mol%, relative to a racemic alcohol. If the content is more than 5 mol%, cost becomes expensive. On the other hand, if it is less than 0.1 mol%, the rate of the reaction becomes too slow.

A method for preparing a chiral ester from a racemic alcohol by dynamic kinetic resolution is described in detail as set forth hereunder.

A mixture of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is reacted in a solvent in the presence of a base shown in Scheme 3,

Scheme 3



(4) (100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such

as a halogen atom and a cyano group.

A reaction condition varies with a structure of ruthenium complex. When the ruthenium complex of formula 6 is used, an oxygen gas is required essentially in the reaction and it is performed at a temperature of 40 to 60℃. Said oxygen gas reacts with phosphine, which is a ligand bonded with ruthenium, to convert to phosphine oxide. When the ruthenium complex of formula 7 is used, the reaction is performed at a temperature of 20 to 40℃. When the ruthenium complex of formula 10 is used, the reaction is performed at a temperature of 20 to 40℃. A base is also required to remove acid generated during the reaction. Said base includes triethylamine or diisopropylethyl amine but it is not limited to these examples.

The ruthenium complex of formula 7 is commercially available and is converted to the ruthenium complex of formula 10 in alcohol/base condition. Therefore, results from the ruthenium complex of formula 7 and the ruthenium complex of formula 10 are almost same.

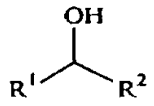
A mechanism of a reaction of a racemic alcohol, ruthenium complex selected from compounds 1, 2 and 3, lipase and an acyl donor compound is described in detail hereunder.

An acyl group supplied from the acyl donor compound is reacted with lipase and this lipase is further reacted with one enantiomer of a racemic alcohol selectively to produce a chiral ester. The other enantiomer is racemized by reacting with ruthenium complex. And further one enantiomer from this racemic alcohol is acylated selectively by lipase and this reaction is repeated to produce optically pure chiral ester with preventing generation of ketone which is a by-product in conventional dynamic kinetic resolution.

Reaction solvent is not limited but it is preferred to use methylene chloride, toluene, benzene, or hexane because a solvent commonly affects

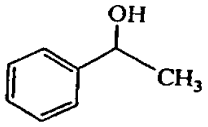
production yield in enzymatic catalysis reaction. An amount of said solvent is used to be 0.2 to 0.3 M concentration of a racemic alcohol.

Said racemic alcohol is generally expressed in the formula 4. It is not limited but examples of the present invention are the following compounds 4a, 4b, 4c, 4d, 4e or 4f,

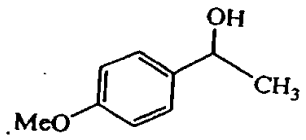


(4)

wherein R^1 and R^2 are the same as defined above.



(4a)



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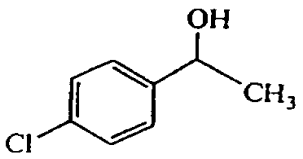

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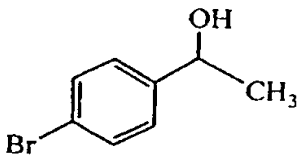

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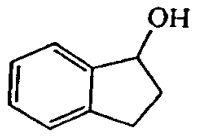

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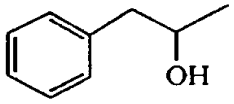


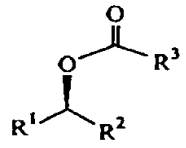
(4f)

Said lipase, which is esterase, acylates one enantiomer from a racemic alcohol selectively to a chiral ester. Examples of lipase are *Pseudomonas cepacias* lipase and *Candida antarctica* lipase and more particulary, *Candida antarctica* component B lipase supported on acrylic resin (Novozym 435, Novo company) or *Pseudomonas cepacias* lipase supported on ceramic particle (lipase PS-C, Amano company). An amount of said lipase is in the range of 10 to 60mg, preferably 30 mg, relative to 1 mmol of an alcohol in Novozym 435 case, and is in the range of 50 to 320 mg, preferably 160 mg, relative to 1 mmol of an alcohol in lipase PS-C case.

Said acyl donor supplies an acyl group to a lipase and acts to move a reaction balance to an acylated product in the presence of a lipase. Preferred acyl donor is aryl ester or alkenyl acetate, the most preferably aryl ester such as *p*-chlorophenyl acetate having electron withdrawing group. An example of alkenyl acetate is isoprophenyl acetate. Such acyl donor compounds are preferred to use because they have an appropriate reactivity without inhibiting racemization. A preferred amount of said acyl donor compound is 2 to 4 equivalents to 1 equivalent of racemic alcohol. If the amount is more than 4 equivalents to 1 equivalent of racemic alcohol, it is difficult to isolate after a reaction. On the other hand, if it is less than 2 equivalents to 1 equivalent of racemic alcohol, the rate of acylation becomes too slow.

A chiral ester expressed in formula 100 is obtained by reacting a racemic

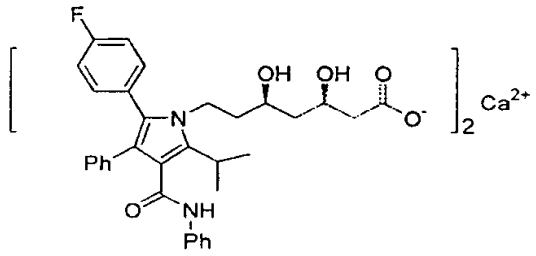
alcohol, a ruthenium complex, a lipase, and an acyl donor compound,



(100)

wherein R^1, R^2 and R^3 are, independently, optionally substituted alkyl, optionally substituted aryl or optionally substituted cycloalkyl group and R^1 and R^2, R^1 and R^3, and R^2 and R^3 can be cyclized each other, where said substituent of alkyl, aryl and cycloalkyl is a hetero atom such as a halogen atom and a cyano group.

The chiral ester of formula 100 of the present invention can be used as a synthetic intermediate for preparing various chiral compounds, chiral pharmaceutical drugs or chiral agrochemicals and more particularly, used as an essential intermediate for preparing Atorvastatin expressed in formula 101 which is a useful drug for treatment for hyperlipemia, L-Carnitine expressed in formula 102 which is as an additive used in food and drugs, and Agenerase expressed in formula 103 which is an essential intermediate of AIDS drug.



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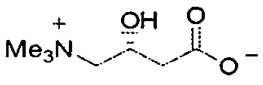

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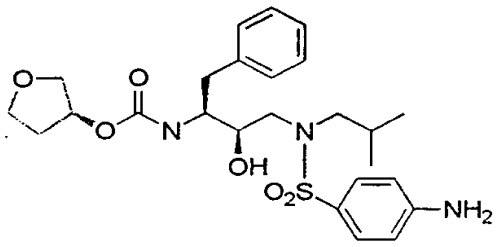

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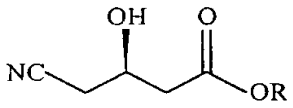
Especially, a chiral compound of formula 100a which is one of the compounds of the present invention is a key intermediate for preparing Atorvastatin of formula 101 disclosed in US Patent No. 5,908,953,



(100a)

wherein R is a low alkyl group.

The process for preparing a chiral ester of formula 100 of the present invention provides minimum production of by-products such as unreacted alcohol residue up to less than 10% and maximum production of product up to 98% having a high optical purity of 99% or more. Because optical purity is the most important factor in preparing chiral compounds for food and pharmaceutical drugs, the chiral ester of the present invention can be used as a useful starting material in various fields, especially fine chemical field.

The following examples are intended to be illustrative of the present invention and should not be construed as limiting the scope of this invention defined by the appended claims.

Example 1

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.75mmol), ruthenium complex of formula 6(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 2.0ml of dichloromethane to give a redish brown suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition. Oxygen(0.0130mmol) was injected with syringe in the reaction suspension and then it was heated at 60℃ for 43 hours.

Examples 2-6

The product, a chiral ester, was prepared by the same procedure of Example 1 except to use racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 7

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 7(0.0130mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

Examples 8-12

The product, chiral ester, was prepared by the same procedure of Example 6 except to use racemic alcohols of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Example 13

A racemic alcohol of formula 4a(0.25mmol), triethylamine(0.25mmol), ruthenium complex of formula 10(0.0100mmol), where X is Cl, 40mg of lipase PS-C, and *p*-chlorophenyl acetate(0.75mmol) were mixed in 1.2ml of methylene

chloride to give a dark redish suspension.

Argon gas was purged into the reaction suspension, after removing oxygen under the vacuum condition and then it was heated at 40℃ for 44 hours.

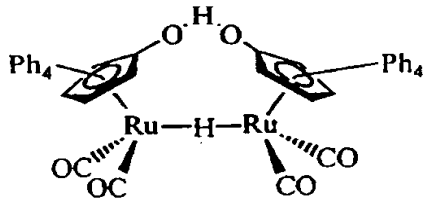
Examples 14-18

The product, chiral ester, was prepared by the same procedure of Example 11 except to use a racemic alcohol of formulas 4b-4f instead of a racemic alcohol of formula 4a.

Comparative Example 1

A racemic alcohol of formula 4a(2mmol), ruthenium complex expressed in the following structure below(0.04mmol), 60mg of Novozym 435, and *p*-chlorophenyl acetate(6mmol) were mixed in 5ml of toluene to give a dark redish suspension.

The reaction suspension was heated at 70℃ for 46 hours under argon gas.



Comparative Examples 2-5

The product, a chiral ester, was prepared by the same procedure of Comparative Example 1 except to use racemic alcohols of formulas 4b, 4d, and 4e and octan-2-ol instead of a racemic alcohol of formula 4a.

Yield, optical purity, and formation of ketone of each reaction of

Examples 1-15 and Comparative Examples 1-5 were determined and tabled in Table 1. Said yield was analyzed by ^{1}H-NMR spectrum, and said optical purity was determined by high performance liquid chromatography. Said ^{1}H-NMR spectrum was taken by using Bruker AM 300 and said high performance liquid chromatography was SpectraSystem P2000.

Table 1

Section	Formation of ketone (%)	Yield (%)	Optical purity (e.e.%)
Example 1	0	85	96
Example 2	0	82	99
Example 3	0	98	99
Example 4	0	91	95
Example 5	0	85	97
Example 6	0	92	96
Example 7	8	90	94
Example 8	10	90	99
Example 9	8	90	99
Example 10	8	92	99
Example 11	8	83	99
Example 12	7	91	98
Example 13	5	95	94
Example 14	7	93	99
Example 15	5	93	97
Example 16	4	96	99
Example 17	4	85	99
Example 18	4	95	99
Comp. Example 1	20	Below 80	-
Comp. Example 2	40	Below 60	-

Comp. Example 3	22	Below 78	-
Comp. Example 4	23	Below 77	-
Comp. Example 5	20	Below 80	-

As shown in Table 1, the amount of a ketone formed as a by-product in Comparative Examples 1 to 5 is in the range of 20 to 40% while that in Examples 1 to 18 is less than 10%. Therefore, the yield of the final product, a chiral ester, prepared by Examples 1 to 18 is much more improved.

As a result, it is proved that the present invention provides a process for preparing an optically pure chiral ester from a racemic alcohol with minimizing the formation of ketone at a high yield in the presence of catalysts which are ruthenium complex selected from formulas 1, 2, and 3, and lipase.